Doc Ophthalmol (2014) 129:17–26
DOI 10.1007/s10633-014-9439-9

ORIGINAL RESEARCH ARTICLE

A frequency-tagging electrophysiological method to identify central and peripheral visual field deficits

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Received: 21 January 2014 / Accepted: 29 April 2014 / Published online: 10 May 2014

Abstract
Background The aim of this study was to develop a fast and efficient electrophysiological protocol to examine the visual field's integrity, which would be useful in pediatric testing.
Methods Steady-state visual-evoked potentials (ssVEPs) to field-specific radial checkerboards flickering at two cycle frequencies (7.5 and 6 Hz for central and peripheral stimulations, respectively) recorded at Oz were collected from 22 participants from 5 to 34 years old and from 5 visually impaired adolescents (12–16 years old). Responses from additional leads (POz, O1, O2), and the impact of gaze deviation on the signals, were also investigated in a subgroup of participants.
Results Steady-state visual-evoked potentials responses were similar at all electrode sites, although the signal from the central stimulation was significantly higher at Oz and was highly sensitive in detecting gaze deviation. No effect of age or sex was found, indicating similar ssVEP responses between adults and healthy children. Visual acuity was related to the central signal when comparing healthy participants with four central visual impaired adolescents. Clinical validation of our electrophysiological protocol was also achieved in a 15-year-old adolescent with a severe peripheral visual deficit, as assessed with Goldmann perimetry.
Conclusions A single electrode over Oz is sufficient to gather both central and peripheral visual signals and

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript, and no one of them received any form of payment to produce the manuscript. There is no conflict of interest. The main findings of the present study have been presented only in a poster form at the 50th ISCEV symposium in Spain in June 2012.

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also to control for gaze deviation. Our method presents several advantages in evaluating visual fields integrity, as it is fast, reliable, and efficient, and applicable in children as young as 5 years old. However, a larger sample of healthy children should be tested to establish clinical norms.

Keywords Visual-evoked potential · Field-specific · Steady state · School-aged children

Introduction

Several medical conditions such as optic nerve disease, pharmacotherapy-related neurotoxicity, or retinopathy might provoke visual field deficits [1–4]. For example, current treatment in severe acute phase of the retinopathy of prematurity involves circumferential ablation of the avascular peripheral retina, which might reduce peripheral vision [5]. In the clinic, the visual field's integrity is commonly investigated by perimetry: patients are presented with bright visual stimuli (either static or dynamic) varying in intensity and location and instructed to report when the stimuli are detected [6]. Although perimetry is considered to be the "gold standard" in visual field assessment, it has several limitations, such as test–retest variability, potential subjective biases (either from the patient or the examiner), and the difficulty of using it in children, as it requires active cooperation and relatively long testing duration [7–9].

Electrophysiological methods for investigating the visual field, such as multifocal electroretinogram (mfERG) and multifocal visual-evoked potential (mfVEP), have been proposed [10–20]. MfERG's and mfVEP's clinical use is nevertheless not optimal, particularly in pediatric populations, since they require relatively long testing time (up to 30 min), they cover a relatively small area of the visual field (up to 30° on either side of the fixation point), and may therefore undervalue the integrity of the peripheral field [21]; again, they require active and steady fixation. Indeed, unstable fixation with small fixation errors (as little as 1° in mfVEP and 6° in mfERG) can cause a dramatic decrease in the foveal signal's amplitude, which can be misinterpreted as a loss of macular function. Eye movement artifacts can also cause saturation of the amplifiers, aberrant drifting, smearing of the responses among different loci, or fluctuation in the central signal [13, 16, 22–24]. Alternately, it has been shown that field-specific VEP provides a more global evaluation of the visual field and its feasibility in children. For instance, field-specific VEPs have been successfully used by Harding et al. [25] and Spencer, Harding [26] to assess the integrity of central and peripheral visual fields in epileptic children treated with vigabatrin, an anti-epileptic drug known for its potential to alter peripheral vision. Stimuli consisted of black and white checks reversing at 0.92 Hz centrally and 1 Hz peripherally, and increasing in size to account for cortical magnification with eccentricity up to 120° of field size. Monocular transient VEPs were recorded from O1 and O2 according to the 10–20 international system of electrode placement [27] and compared with either Goldmann [25] or Humphrey [26] perimetry responses. Results showed good sensitivity (75 %) and specificity (85 %) of VEPs for identifying peripheral visual field impairment. Although this approach is powerful, its current clinical application is not optimal. First, monocular responses were tested one after the other in a counterbalanced manner by recording transient VEPs, which have slow temporal rates of presentation and require a relatively high number of trials to ensure reliable responses. Long testing duration is well known to increase the risk of fatigue and inattention in children. Second, visual fixation in clinical settings is commonly monitored by a technician who identifies periods of poor fixation or lack of concentration, thus interrupting the recordings and prolonging the testing. Finally, responses in Harding et al.'s studies were recorded over O1 and O2 but as far as central and peripheral visual fields are concerned, there is currently no standard recommendation regarding electrode placement. The only potential guide in this matter is that the retinotopic organization of V1 dictates that the activation of the central visual field originates from the occipital pole, whereas the representation of the peripheral vision is located deeper along the calcarine sulcus [28, 29]. Therefore, one might ask whether an electrode placed over Oz would be sufficient to record central and peripheral responses, or, in other words, are electrodes over O1 and O2 really necessary? This is an important question in testing young children, where a minimal duration for electrode setup is desired.

In an attempt to address these issues, we undertook field-specific electrophysiological assessment by using steady-state visual-evoked potentials (ssVEPs). By contrast with the transient approach, ssVEPs

permit the measurement of visual functions in a short period of time (in the second scale rather than the minute scale), making it a potentially valuable tool for probing visual processing in individuals of limited attention span [30]. The possibility of presenting different stimulations simultaneously and tracking the respective response through spectral analyses (e.g., fast Fourier transformation) makes ssVEPs highly valuable for visual assessment in pediatric population. For example, Allen et al. [31] assessed grating acuity and contrast sensitivity in infants using stimuli (a circular stimulus in the center subtending 4° and a semicircular stimulus from 8 to 16°) flickered at 6 and 8 Hz to test the central and peripheral visual fields. The use of these frequencies was justified for several reasons. First, the authors showed that the estimated visual acuity was the same with either frequency and, in fact, not significantly different with any frequency from 2 to 20 Hz. Second, the use of closely spaced and relatively low temporal frequencies prevents measurement biases (i.e., not related to the visual function) caused by the stimulation of different and/or immature temporal mechanisms. This is in line with the previous ssVEP studies showing that stimulations at frequencies below and close to 10 Hz, i.e., in the low range region according to Regan's classification [30], produce high-amplitude responses [32–34].

The goal of the present study was to improve the field-specific VEP assessment initially proposed by Harding and coworkers [25, 26, 35] by developing and validating a fast and efficient ssVEP protocol that would be useful in pediatric testing. We first aimed to evaluate whether or not responses from an electrode placed over Oz would adequately reflect central and peripheral visual brain activity by carefully controlling for eye movements in adults. The second objective was to specifically apply the protocol in school-aged and visually impaired participants and also to examine how the ssVEPs can predict visual acuity.

Methods

Participants

We recruited 22 healthy participants with normal or corrected vision aged from 5 to 34 years (mean = 17.14; SD = 9.05) and 5 adolescents with a visual deficit from the Ophthalmology Department at Sainte-Justine Hospital University Center. As shown in Table 1, 4 of the 5 adolescents (mean age = 14.4; SD = 1.5) had a central visual impairment while the fifth one had only a peripheral visual deficit as assessed by Goldmann perimetry due to the presence of tubers in the anterior calcarine cortex and/or vigabatrin intake (mean dose = 48.91 mg/Kg/day; duration = 4 years) at young age. Because some participants had unbalanced monocular visual acuities and the ssVEPs in the present study were conducted binocularly, a binocular visual acuity index was estimated based on the algorithm initially proposed by the American Academy of Ophthalmology [36]: ((3 × best eye value) + worse eye value)/4. Although this index is still recognized to provide a good quantitative estimation of the visual function impairment, it does not take into account binocular interactions (summation or inhibition) [37–39]. This study was approved by the Ethic's Committee of the Sainte-Justine Hospital University Center. Informed consent was obtained in writing from all participants or their guardians, or assent from the participant themselves when possible.

Table 1 Sociodemographic data of five visually impaired adolescents

Age	Sex	Diagnostic	Snellen VA[a]		Binocular VA index[a]
			O.D.	O.S.	
12	M	Best disease	20/32	20/200	−0.325
14	M	Best disease	20/50	20/40	−0.375
15	F	RP[b]	20/50	20/70	−0.4375
16	F	Unspecified maculopathy	20/400	20/80	−1.075
15	M	West syndrome[c]	20/20	20/20	0.45

[a] *VA* visual acuity

[b] *RP* retinitis pigmentosa

[c] Normal central visual acuity with a severe peripheral deficit

Stimuli

Similarly to Harding et al. [25], two high-contrast (96 %) radial checks with a central stimulation at 0–5° diameter and a peripheral stimulation at 30–60° radius were presented to the participants (Fig. 1a). Thus, both regions of the stimulation were quite distant, avoiding any lateral interaction [40]. The stimulus mean luminance was 50 cd/m^2. A colored dot that alternated colors randomly (between yellow and green) was

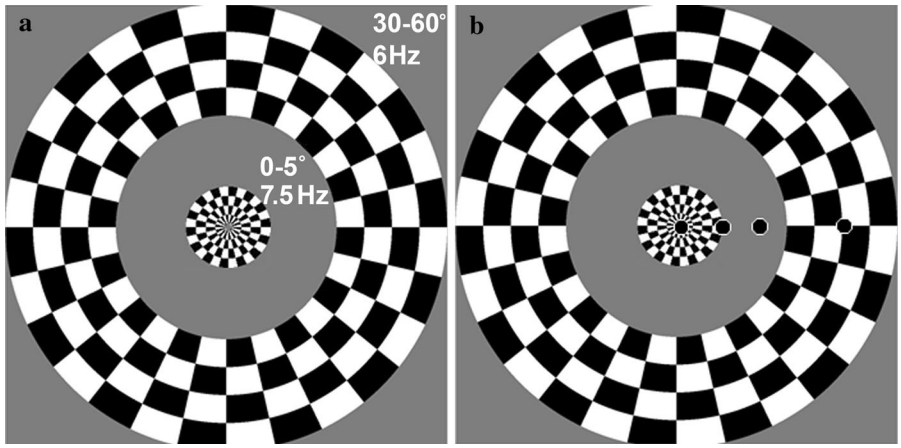

Fig. 1 Stimulation (**a**) was made of two *concentric circles* (0–5 and 30–60° of angle). *Inner circle* oscillates at 15 reversals/s (7.5 Hz) and *outer circle* flickers at 12 reversals/s (6 Hz) at high contrast (96 %). Adult participants were instructed to stare at each fixation dot (0, 5, 17, and 42°) (**b**) one after the other for a 30-s block repeated twice

presented in the middle of the computer screen in order to keep the participant's attention, and to ensure quality data. SsVEPs were used for their fast and reliable responses, including in very young children [31, 41–47]. The inner and outer stimulus areas flickered at two distinct cycle frequencies that are 7.5 Hz for the inner checks (corresponding to an alternation frequency of 15 Hz) and 6 Hz for the outer checks (corresponding to an alternation frequency of 12 Hz). These two frequencies evoke good VEP responses in infants and children and yield very similar results for estimating visual function [31].

Experimental procedure

Participants underwent electroencephalogram (EEG) recordings under a meso-to-photopic viewing condition to ensure that no other light source would affect the visual stimulation's contrast. Stimuli were presented binocularly on a 30″ LCD monitor (DELL, model 3007WFP) from a distance of 20 cm, using a chin rest and controlled by Presentation software (Neurobehavioral Systems, Inc., San Paolo, CA). VEPs were recorded with Ag–AgCl electrodes using a V-Amp system (BrainVision Products, Inc., Munich, Germany) to measure central and peripheral visual field responses. Electrodes were placed according to the international 10–20 system over the visual cortex at Oz, POz, O1, and O2 in adults, but only at Oz in children (<18 years old). Reference and ground electrodes were located at Fz and on the forehead, respectively. Left and right ocular electrodes were placed on the lower eyelids, and canthi electrodes were added to control for ocular movements in children. During EEG recordings, all participants were instructed to stare at the fixation point located in the center of the screen during two 30-s blocks. In the adult experiment, participants were instructed to stare at four different fixation points (0, 5, 17, and 42° of eccentricity), one after the other, for 30 s (Fig. 1b). The task was performed twice in a counterbalanced manner (i.e., from 0 to 42° and from 42 to 0°). Participants were allowed to take breaks between each block if needed.

Data analysis

Electroencephalogram (EEG) analyses were performed with *Analyzer 2* software (Brain Products, Inc., Munich, Germany). Artifact rejection took place by withdrawing automatically detected segments with high amplitude (≥100 μV) or blinks. An additional procedure was conducted to remove eye movement artifacts using complex demodulation, which allows the tracking of the signal's amplitude over time as a function of the fixation point deviation. Indeed, signal recorded from central stimulation is known to be a good marker of the gaze deviation [31]. The whole EEG recording was divided into two-second EEG segments (i.e., 15 segments for each 30-s block). An EEG segment was rejected from the analysis if the signal's amplitude from the central stimulation was lower than the signal's amplitude from the peripheral stimulation, or larger than one standard deviation of the mean signal from the central stimulation for more than 1 s.

The central and peripheral stimulation responses were measured by performing a fast Fourier transformation (FFT) at the alternation frequencies or second

harmonics (i.e., 12 and 15 Hz, respectively). A Hanning window of 10 % was used on the data, and the number of data points per sweep was set to 1,024. The spectral resolution was 0.5 Hz. FFT allows for the differentiation between the central and peripheral stimulus regions, since the responses are resolvable by the spectrum analysis [32]. The noise level was calculated based on the average of two neutral frequencies close to the frequencies of interest, which are 13.5 and 16.5 Hz [31, 48].

Statistical analysis

Statistical analyses were carried out using SPSS software package version 18.0 (SPSS Inc., Chicago, IL). In all the analyses of variance (ANOVAs), if the sphericity assumption was violated, Greenhouse–Geisser-corrected p values were reported with original degrees of freedom. Post hoc analyses were carried out by using Fisher's least significant difference among means. Paired t test was used for the test–retest validation since two repeated samples were gathered. Moreover, Cronbach's alpha coefficient allowed measuring the internal consistency of our method. Comparing healthy participants with the visually impaired ones was possible using Spearman's correlation and Mann–Whitney U test.

Results

The effects of electrode sites (Oz, POz, O1, and O2), fixation points (0, 5, 17, and 42°), and alternation frequencies (12 and 15 Hz) on the VEP responses were first assessed in 10 young adults (mean age = 25.9 years; SD = 4.1) using repeated-measure ANOVAs. Results revealed a significant triple interaction Fixation × Electrode × Frequency (F (9; 81) = 3.97, $p = 0.019$). Follow-up ANOVAs revealed two significant interactions. First, an Electrode × Frequency interaction (F (3; 27) = 5.84, $p = 0.002$) with a main effect of electrode (F (3; 27) = 3.48, $p = 0.039$) was found (Fig. 2). The central response at Oz (mean = 5.76 μV^2; SD = 4.85) was significantly greater than POz (mean = 2.13 μV^2; SD = 1.82) and O1 (mean = 2.64 μV^2; SD = 3.76), and close to the significance level ($p = 0.06$) in regard to O2 (mean = 2.82 μV^2; SD = 2.65). Although the response to peripheral stimulation was lower than the central one at Oz (2.06 vs. 5.76 μV^2), it did not differ from the other electrodes. Second, a Fixation × Frequency interaction (F (3; 27) = 11.99; $p = 0.006$) with a main effect of fixation (F (3; 27) = 9.75, $p = 0.008$) was found (Fig. 3). A gaze shift of 5° or more from the central (0°) location significantly decreased the amplitude of the central stimulation on all electrodes, but not of the peripheral stimulation. The maximal 0°–5° reduction was observed at Oz with a factor of 6.9 (5.76 vs. 0.84 μV^2). Because Oz responses did not differ from the other electrodes, only Oz was used in further analyses. The reliability of the recordings at Oz was tested using a paired t test to compare the responses collected during the two 30-s blocks. No significant difference between the blocks was found, either for the signal from the peripheral (2.23 vs. 1.88 μV^2, t (9) = 0.84, $p = 0.42$) or the central stimulation (5.86 vs. 5.66 μV^2, t (9) = 0.52, $p = 0.62$), which means they are not correlated. Moreover, the internal consistency measured with Cronbach's alpha was high for both signals (central = 5.86 vs. 5.66 μV^2, α = 0.87 and peripheral = 2.23 vs. 1.88 μV^2, $\alpha = 0.86$), meaning that both parts of the stimulation have good reliability. Mean signal-to-noise ratio (SNR) was 7.6:1 (ranging from 2.9 to 14.9) and 21:1 (ranging from 2.2 to 56.3) for signals from peripheral and central stimulations, respectively.

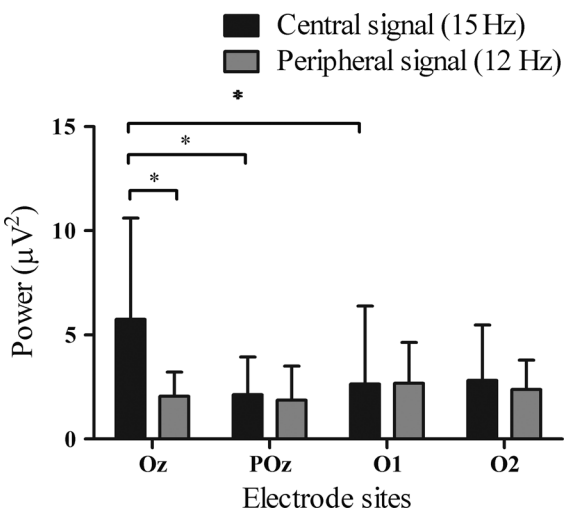

Fig. 2 Oz shows a higher signal from the central stimulation than POz and O1 but does not differ from O2. Oz is the only electrode site to show a significantly higher central signal than the peripheral one

Based on the results from the adults, only Oz recording was used to test the protocol in child

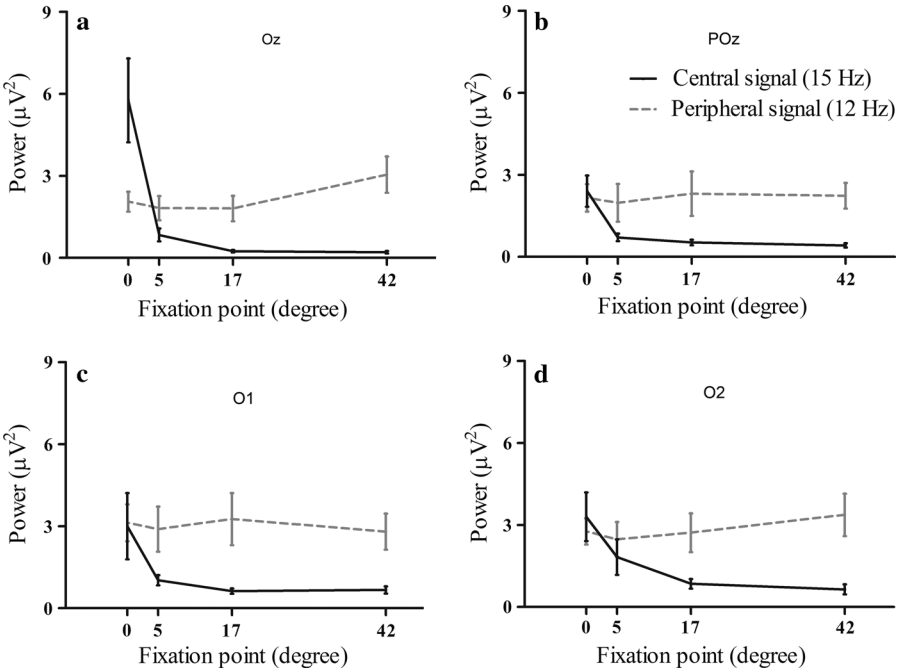

Fig. 3 Signal from the central stimulation significantly and drastically drops between the natural fixation point (0°) and all of the others (5, 17, and 42°). No such differences are found in peripheral signal, which slowly increases as the regard deviates from the center to the periphery

participants. A sample of 12 children from 5 to 15 years old (mean age = 9.8 years; SD = 3.8) underwent the experiment. As found in the adult experiment, no significant difference between the blocks was found, either for the peripheral (1.83 vs. 2.07 μV^2, t (11) = −0.774, $p = 0.46$) or the central stimulation (8.54 vs. 7.09 μV^2, t (11) = 1.25, $p = 0.24$), with a Cronbach's alpha of 0.93 and 0.91, respectively. Mean signal-to-noise ratio (SNR), which is 5.5:1 (ranging from 2 to 16.9) and 14.3:1 (ranging from 1.9 to 59.8) for responses from peripheral and central stimulations, respectively, was not significantly different ($p > 0.05$) than those measured in adults. Correlation analyses in all participants revealed that neither age nor sex were related to the signal from the peripheral ($r = -0.124$; $p = 0.58$ and $r = 0.414$; $p = 0.06$, respectively) or the central stimulation ($r = -0.150$; $p = 0.50$ s and $r = -0.010$; $p = 0.963$, respectively).

Since there was no significant correlation between responses, age, and sex, all the healthy participants (i.e., adults and children, $n = 22$) were pooled and compared to the four adolescents with central visual deficit in order to test the hypothesis that ssVEPs differ between the two groups. A Mann–Whitney test revealed that the responses from central stimulation between participants with abnormal visual acuity (mean = 0.2 μV^2) and normal visual acuity (mean = 6.3 μV^2) were indeed significantly different (U = 5.0, z = −2.71, $p = 0.003$). More importantly, Spearman's correlation showed that the binocular visual acuity was well predicted by the ssVEPs (rho = 0.56; $p = 0.003$). To further verify the validity of our method, electrophysiological testing was administrated to a 15-year-old adolescent with a severe peripheral visual deficit. The ssVEPs of the four central visual impaired participants and the peripheral visual impairment patient are illustrated in Fig. 4. In accordance with this Goldmann perimetry assessment (Fig. 4c), the ssVEP response of the peripheral patient was detectable for central stimulation but not for peripheral stimulation (Fig. 4b). Indeed, paired t tests revealed a significant response to central stimulation compared to the noise level (mean response at 13.5 and 16.5 Hz) (t (19) = 8.77, $p < 0.05$), whereas no such significant difference was found regarding peripheral stimulation (t (19) = 0.53, $p = 0.60$). When compared to normal vision participants, the response from peripheral stimulation in this patient was below the first centile.

Discussion

The aim of this study was to develop a fast and efficient electrophysiological protocol, which could be

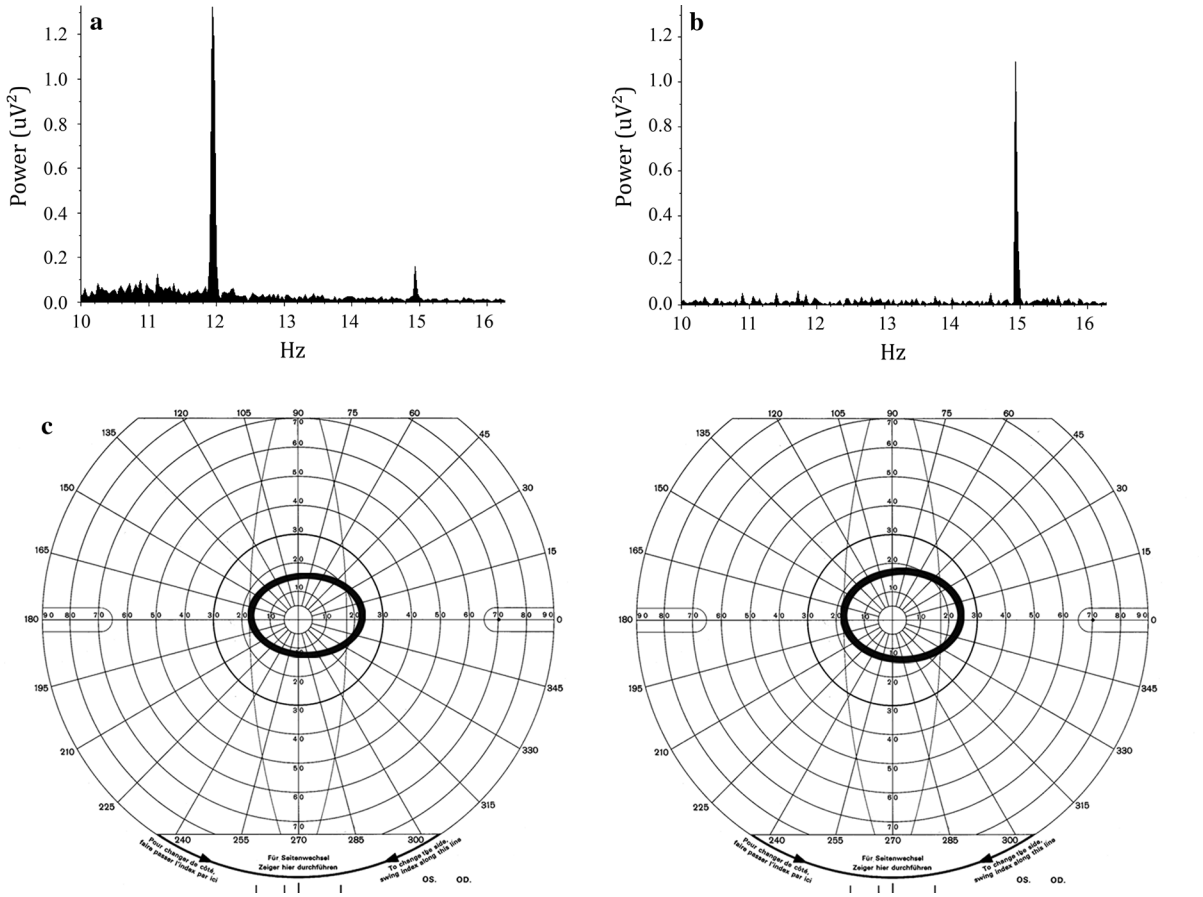

Fig. 4 FFT from central and peripheral stimulations gathered at Oz for 4 central visually impaired adolescents (**a**) and one peripheral visual impaired adolescent (**b**). Clinical assessment (Goldmann perimetry) of peripheral vision conducted in the same adolescent (**c**)

applied to pediatric testing, and to examine the visual field's integrity. Results showed that Oz gathered significantly higher signals from the central stimulation, and that the responses to the peripheral stimulation were similar on all electrode sites. In addition, Oz appears to be a good proxy to track central fixation, since the reduction in the signal from the center of the stimulation as a function of gaze deviation was maximal. The clinical validation of our electrophysiological protocol was evidenced in visually impaired adolescents where deficits in visual acuity decreased the ssVEP response to central stimulation and where a clinical diagnostic of concentric vision was linked to the absence of brain response in peripheral visual field.

In this study, we examined the impact of ocular movement on signal from peripheral and central stimuli, as it is a crucial aspect in visual field assessment and often represents a major methodological challenge in pediatric testing. The quantification of the ocular movements demonstrated that the central signal was particularly sensitive to gaze deviation starting at 5° of angle. Our results concur with those of Allen et al. [31], who observed a great decrease in the signal-to-noise ratio from the center of the stimulation (by a factor of 3.2), and a smaller increase in the peripheral signal-to-noise ratio (by a factor of 2.3) when the fixation point moved sideways (5° of angle) in child testing. The fact that the central signal is very sensitive to gaze deviation was successfully exploited in the present study to track the signal from the central stimulation over time by using complex demodulation analysis, thus improving the artifact rejection process.

The use of 6- and 7.5-Hz cycle frequency stimulations in our ssVEP protocol was efficient in assessing the integrity of both central and peripheral visual fields in a short amount of time (30 s), with consistent test–retest

validity in both adults and children. In addition to the fact that these frequencies are associated with good responses [30, 32–34], they are desirable in the clinical settings as they are below the alternation frequency limit (15–25 Hz), which is more likely to induce photic or pattern stimulation seizures [49]. One clinical limitation in our study is that only two main regions of the visual field (central and peripheral) were tested. In a recent ssVEP study in adults, Abdullah et al. [20] succeeded in "dissecting" the visual field into 9 different regions simultaneously, using temporal frequencies ranging from 18.29 to 21.56 Hz. It would be of interest in the future to investigate whether a similar approach could be developed with lower temporal frequencies.

By contrast to Harding et al. [25], and in accordance with Abdullah et al. [20], we suggest that one electrode placed at Oz is sufficient to record signals from both central and peripheral visual field stimulations. The use of other electrodes to pick up peripheral signal is indeed not necessary considering the absence of significant differences with Oz. Note that the slight imbalance observed between O1 and O2 for the signal from the central stimulation is in agreement with the results of Rebai et al. [50] and Rebai et al. [51], who demonstrated that the right hemisphere tends to show larger VEP amplitude. It is not clear, however, why the amplitudes of the central and peripheral responses at Oz were so different. It is quite possible that activation of the central visual field at the occipital pole is better picked up by the Oz lead, in comparison with the peripheral signal, which originates deeper in the calcarine fissure. Furthermore, the fixation point may have engaged attention at the central stimulus, which can either enhance the ssVEP response of the "attended" (central) stimulus or reduce the ssVEP response of the "unattended" (peripheral) stimulus [52, 53]. In line with the latter possibility, a recent study has shown that peripheral response is reduced when the observers are explicitly instructed to pay attention to the center when the peripheral stimulus is contiguous with the central one [54]. Such an attention modulation in the present study was unlikely since the task was passive (no explicit attention instruction was given) and the two visual stimulations were not contiguous.

Allen et al. [31] also used simultaneous stimulation of central and peripheral visual fields to assess visual acuity and contrast sensitivity in 39 infants. However, these authors found important inter-subject variations, especially when it came to the presentation of small-diameter stimuli. We also found this kind of variation. By contrast to the pattern-reversal stimulation, as used here, there is some indication in the literature suggesting that onset–offset stimulation is more effective in reducing variability [55, 56], even though pattern-reversal stimulation may be more suitable in some experimental situations such as pattern electroretinogram (PERG), which are more susceptible to luminance artifacts [34].

The comparison of adult' and child's responses to our ssVEP field-specific stimulation showed no significant difference between both groups, which indicates that the ssVEP responses are similar across sex and age, at least from 5 years old to adult age. Moreover, responses to the central stimulation predicted the binocular visual acuity. The examination of a peripherally visually impaired adolescent's responses confirmed the validity of our protocol since it concurs with a previous clinical evaluation.

To conclude, our electrophysiological protocol appears to be a promising method to evaluate the visual field's integrity, not only in healthy children and adults but also in a pediatric, visually impaired population. For example, as Good [57] suggested, follow-up should be considered to investigate the maturation of the retina in infants treated (or not) for retinopathy of the prematurity since it is known that rod function is altered [58] and that circumferential ablation of the avascular peripheral retina is common use in that disease [5]. Our protocol presents several advantages, such as the simultaneous assessment of central and peripheral visual fields, with a single electrode placed over Oz, thus rendering the task duration short. It also covers a large visual field (up to 60° in each hemifield) and allows comfortable visual evaluation of gaze deviation. Further investigation in a larger sample of healthy children should help establish clinical norms, as our field-specific VEP method is easily feasible in children as young as five years old and as it is related to visual acuity.

Acknowledgments We would like to thank Mathieu Simard for his very helpful assistance in data collection and analysis. This research was funded by The Vision Health Research Network of the FRQS and The Quebec Foundation for the Blind.

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